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(54) Title: AMORPHOUS CITALOPRAM

(57) Abstract: Citalopram base is purified and isolated by chromatography.

AMORPHOUS CITALOPRAM

This invention relates to a pharmaceutical product, more particularly to citalopram.

Citalopram is a well known antidepressant drug whose systematic name is 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile. It is a selective centrally acting serotonin (S-hydroxytryptamine; 5-HT) reuptake inhibitor. It is marketed as the hydrobromide or hydrochloride salt.

Citalopram was first described in GB-A-1526331 and, subsequently, a number of different processes have been described for its preparation. In many of these, the final step is to introduce the 5-cyano group but there have been problems in purifying the final product to remove intermediates and by-products. Among the purification processes used has been isolation of the free base as an oil (bp 175°C/0.03 mm Hg) and subsequent thin film distillation followed by conversion to the desired salt. Another purification process involves conversion to a salt and recrystallisation thereof. Neither of these techniques has been particularly satisfactory.

Recently, another purification procedure has been described in GB-B-2357762. Here, citalopram base is set free and precipitated in crystalline form, and after optional recrystallisation for purification, converted to the desired salt. This process is said to be particularly effective at removed 5-substituted intermediate contaminants. A disadvantage of this is that it requires repeated crystallisations to achieve high purity and this is undesirable.

We have now found another way of purifying citalopram which has a number of advantages over prior known processes:

In accordance with one aspect of the present invention, crude citalopram is purified by chromatography, preferably liquid chromatography. We have found that, in this way, satisfactory purification can be achieved in a simple manner.

In another aspect of the invention, we have found that a previously undescribed

form of citalopram base, namely amorphous citalopram base, has excellent utility. Thus, the invention provides amorphous citalopram base *per se*, including amorphous S-citalopram base.

According to a particularly preferred aspect of the invention, citalopram purified by chromatography, is converted to the amorphous base and, optionally, as desired, to the desired salt.

In the process of the present invention, citalopram is separated from (ie isolated from) impurities, preferably on a single column without multiple elutions. This is a commercial scale operation resulting in purified citalopram. This is quite different from for example, laboratory techniques for determining citalopram and its metabolites in plasma, which types of procedure use an analytical HPLC column and are not a preparatory method, and do not result in isolation of the product but rather its estimation in solution.

The crude citalopram which can be purified by chromatography in accordance with the present invention may have been made in any way such as, for example, by any of the methods known in the art. The purification method is particularly useful with crude citalopram made by a step including exchange of a 5-halo substituent by a 5-cyano substituent using, for example, sodium, potassium, cuprous or zinc cyanide, with or without catalysts or solvents.

Any suitable form of chromatography can be used including, for example, medium pressure liquid chromatography (MPLC), high performance liquid chromatography (HPLC), or simulated moving bed chromatography (SMB).

Thus, for example, crude citalopram may be loaded on MPLC with a suitable stationary phase for normal or reverse phase chromatography. The product from this purification procedure is substantially free of all the known impurities of citalopram such as the 5-carboxamide impurity, 5-chloro impurity, 5-bromo impurity and the N-desmethyl impurity. Typically the level of each of these impurities in the purified citalopram is less than 0.1%.

Alternatively, preparative HPLC can be used, employing a suitable stationary phase and mobile phase, or SMB can be used with a suitable stationary phase and mobile

phase. These techniques are well known in the art and further description thereof will not therefore be given.

The purified citalopram base resulting from the chromatography will be in solution in the eluant. It can then be recovered as the base, if desired. Thus, for example, it may be recovered as the oil or in crystalline form. Preferably, however, in accordance with a feature of the present invention, it is recovered as the amorphous base. This can be effected in a number of ways such as by lyophilisation or evaporation (eg by a rotary evaporation), as will be clear to those skilled in the art. We prefer, however, to use spray drying to obtain the amorphous citalopram base.

Salts of the purified base can be made by routine procedures either directly from the eluate solution, or from the amorphous base, or by any other route as desired. The preferred salts are the hydrobromide, hydrochloride and oxalate, but others can of course be made.

In order that the invention may be more fully understood, the following Examples are given by way of illustration only.

Example 1

Crude citalopram base 10 g is dissolved in 20 ml dichloromethane and loaded on a column containing silica gel 60 - 120# (300 g) and eluted with a gradient mixture of dichloromethane, toluene and methanol. The eluent was monitored by HPLC and the fractions containing pure citalopram were concentrated to obtain an oil. Purity of the oil was 99.5%

Example 2

Crude citalopram base 10 g is dissolved in 20 ml toluene and loaded on a column containing neutral alumina (300 g) and eluted with a gradient mixture of toluene and dichloromethane. The eluent was monitored by HPLC and the fractions containing pure citalopram were concentrated to obtain an oil. Purity of the oil was 99.5%

Example 3

Crude citalopram base 20 g is dissolved in 20 ml dichloromethane and loaded on a MPLC column 90 mm x 1500 mm containing silica gel 30-40 microns and eluted with a gradient mixture of dichloromethane toluene and methanol. The fractions containing pure

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citalopram were concentrated to obtain an oil. Purity of the oil was 99.5%.

Example 4

Crude citalopram base 20 g is dissolved in 20 ml acetonitrile and loaded on a MPLC column 90 mm x 1500 mm packed with RP 18, 40 - 60 micron and eluted with a gradient mixture of acetonitrile and water. The fractions containing pure citalopram were concentrated to obtain an oil. Purity of the oil was 99.5%.

Example 5

The oil from Example 1 was dissolved in methanol to obtain a 10% solution. This was spray dried on a Lab-Plant spray drier SD-05 with an inlet temperature of 80°C and outlet temperature of 45°C at a feed rate of about 10ml/min to obtain a fine amorphous solid which was characterised by powder x-ray diffraction.

Example 6

The oil obtained from Example 2 was dissolved in ethyl acetate (5v/w) and treated with aqueous hydrobromic acid 48% to a pH of about 3.5. The solids were filtered and dried to obtain citalopram hydrobromide.

CLAIMS:

- 1 Amorphous citalopram base.
- 2 A method of purifying citalopram base which comprises subjecting it to chromatography.
- 3 A method according to claim 2, wherein the citalopram base is purified by liquid chromatography.
- 4 A method according to claim 3, wherein the base is purified by medium or high pressure liquid chromatography or by simulated moving bed chromatography.
- 5 A method according to claim 2, 3 or 4, wherein the purified base is recovered as an oil.
- 6 A method according to claim 2, 3 or 4, wherein the purified base is recovered as a solid.
- 7 A method according to claim 6, wherein the purified base is recovered as amorphous base.
- 8 A method according to claim 7, wherein the amorphous base is prepared by spray drying the purified base.
- 9 A method of making a salt of citalopram which comprises converting amorphous citalopram base into a salt.
- 10 A method according to claim 9, wherein the amorphous base has been made by the method of claim 7 or 8.

11 A method of making a salt of citalopram which comprises purifying citalopram by the method of any of claims 2 to 8, and converting the purified base to a salt.

12 A method of making amorphous citalopram base which comprises spray drying a solution of the base.

13 A method of making amorphous citalopram base, which comprises lyophilisation.

14 A method according to claim 12 or 13, wherein the solution contains base which has been purified by chromatography.

15 A salt of citalopram made from amorphous citalopram base.

16 A salt of citalopram made by the method of 9, 10 or 11.

17 A pharmaceutical composition which comprises amorphous citalopram base, or a salt of citalopram as claimed in claim 15 or 16.

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B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GB 2 357 762 A (LUNDBECK & CO AS H) 4 July 2001 (2001-07-04) cited in the application page 5, line 20-31; claims ---	1-17
A	WO 01 68627 A (PETERSEN HANS ; HOLM PER (DK); BOEGESOE KLAUS PETER (DK); LUNDBECK) 20 September 2001 (2001-09-20) page 5, line 20-31; claims ---	1-17
		-/-

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>CHEMICAL ABSTRACTS, vol. 126, no. 3, 20 January 1997 (1997-01-20) Columbus, Ohio, US; abstract no. 26304, HAUPT D.: "Determination of citalopram enantiomers in human plasma by liquid chromatographic separation on a chiral-AGP column" XP002225392 abstract & J. CHROMATOGR., B: BIOMED. APPL., vol. 685, no. 2, 1996, pages 299-305, ---</p>	1-17
A	<p>CHEMICAL ABSTRACTS, vol. 105, no. 10, 8 September 1986 (1986-09-08) Columbus, Ohio, US; abstract no. 85185, FUKUYAMA Y. ET AL: "Phtalimides from Ligusticum wallichii" XP002225344 abstract & JP 61 007267 A (OTSUKA PHARM. CO., LTD.) 13 January 1986 (1986-01-13) ---</p>	2-4

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intel onal Application No

PCT/GB 03/00810

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB 2357762	A 04-07-2001	AT 4364 U1 AT 223396 T AU 746664 B2 BE 1013210 A3 BR 0109373 A CA 2360287 A1 CH 691477 A5 CH 691537 A5 CZ 20010808 A3 DE 1227088 T1 DE 10108042 A1 DE 20121240 U1 DE 60100022 D1 DE 60100022 T2 WO 0168627 A1 DK 1169314 T3 DK 173903 B1 EP 1169314 A1 EP 1227088 A1 ES 2173054 T1 ES 2180471 T1 ES 2159491 A1 FI 20010225 A FR 2806086 A1 GR 1003796 B2 IT MI20010406 A1 NL 1017413 C1 NO 20010619 A NO 20020356 A PT 1169314 T SE 517136 C2 SE 0103046 A SI 1169314 T1 TR 200202185 T2	25-06-2001 15-09-2002 02-05-2002 02-10-2001 24-12-2002 20-09-2001 31-07-2001 15-08-2001 16-01-2002 06-02-2003 18-10-2001 04-07-2002 10-10-2002 06-03-2003 20-09-2001 14-10-2002 11-02-2002 09-01-2002 31-07-2002 16-10-2002 16-02-2003 01-10-2001 14-09-2001 14-09-2001 08-02-2002 28-08-2002 13-09-2001 14-09-2001 14-09-2001 29-11-2002 16-04-2002 14-11-2001 31-12-2002 23-12-2002
WO 0168627	A 20-09-2001	AT 4364 U1 AT 223396 T AU 746664 B2 BE 1013210 A3 BR 0109373 A CA 2360287 A1 CH 691477 A5 CH 691537 A5 CZ 20010808 A3 DE 1227088 T1 DE 10108042 A1 DE 20121240 U1 DE 60100022 D1 DE 60100022 T2 WO 0168627 A1 DK 1169314 T3 DK 173903 B1 EP 1169314 A1 EP 1227088 A1 ES 2173054 T1 ES 2180471 T1 ES 2159491 A1 FI 20010225 A	25-06-2001 15-09-2002 02-05-2002 02-10-2001 24-12-2002 20-09-2001 31-07-2001 15-08-2001 16-01-2002 06-02-2003 18-10-2001 04-07-2002 10-10-2002 06-03-2003 20-09-2001 14-10-2002 11-02-2002 09-01-2002 31-07-2002 16-10-2002 16-02-2003 01-10-2001 14-09-2001

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int'l Application No

PCT/GB 03/00810

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0168627	A	FR 2806086 A1 GB 2357762 A ,B GR 1003796 B2 IT MI20010406 A1 NL 1017413 C1 NO 20010619 A NO 20020356 A PT 1169314 T SE 517136 C2 SE 0103046 A SI 1169314 T1 TR 200202185 T2	14-09-2001 04-07-2001 08-02-2002 28-08-2002 13-09-2001 14-09-2001 14-09-2001 29-11-2002 16-04-2002 14-11-2001 31-12-2002 23-12-2002
JP 61007267	A	13-01-1986	NONE